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Clinical Investigation

The Efficacy and Safety of Conventional and Hypofractionated High-Dose Radiation Therapy for Prostate Cancer in an Elderly Population: A Subgroup Analysis of the CHHiP Trial

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Summary

The efficacy and toxicity of radiation therapy for localized prostate cancer in CHHiP (Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer) trial participants aged ≥ 75 years was compared with patients aged < 75 years. There was no evidence of a difference in biochemical or clinical recurrence–free survival or clinically significant toxicity between the older and younger patient groups. Hypofractionated radiation therapy is an effective and well-tolerated treatment for localized prostate cancer in an elderly population with good performance status.

Purpose: Outcome data on radiation therapy for prostate cancer in an elderly population are sparse. The CHHiP (Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer) trial provides a large, prospectively collected, contemporary dataset in which to explore outcomes by age.

Methods and Materials: CHHiP participants received 3 to 6 months of androgen deprivation therapy and were randomly assigned (1:1:1) to receive 74 Gy in 37 fractions (conventional fractionation), 60 Gy in 20 fractions, or 57 Gy in 19 fractions. Toxicity was assessed using clinician-reported outcome (CRO) and patient-reported outcome questionnaires. Participants were categorized as aged < 75 years or ≥ 75 years. Outcomes were compared by age group.

Results: Of 3216 patients, 491 (15%) were aged ≥ 75 years. There was no difference in biochemical or clinical failure rates between the groups aged < 75 years and ≥ 75 years for any of the fractionation schedules. In the group aged ≥ 75 years, biochemical or clinical failure–free rates favored hypofractionation, and at 5 years, they were 84.7% for 74 Gy, 91% for 60 Gy, and 87.7% for 57 Gy. The incidence of CRO (grade 3) acute bowel toxicity was 2% in both age groups. The incidence of grade 3 acute bladder toxicity was 8% in patients aged < 75 years and 7% in those aged ≥ 75 years. The 5-year cumulative incidence of CRO grade ≥ 2 late bowel side effects was similar in both age groups. However, in the group aged ≥ 75 years, there was a suggestion of a higher cumulative incidence of bowel bother (small or greater) with 60 Gy compared with 74 Gy and 57 Gy. Patient-reported bladder bother was slightly higher in the group aged ≥ 75 years than the group aged < 75 years, and there was a suggestion of a lower cumulative incidence of bladder bother with 57 Gy compared with 74 Gy and 60 Gy in patients aged ≥ 75 years, which was not evident in those aged < 75 years.

Conclusions: Hypofractionated radiation therapy appears to be well tolerated and effective in men aged ≥ 75 years. The 57-Gy schedule has potential advantages in that it may moderate long-term side effects without compromising treatment efficacy in this group.

Introduction

Prostate cancer (PCa) is the most common cancer in men in the United Kingdom, with 46,690 new cases and 11,287 deaths in 2014 (1). Fifty-four percent of all new cases of PCa are diagnosed in men aged > 70 years, with the highest incidence in men aged > 90 years (1). Management options for localized disease include active surveillance in patients with low-risk disease, external beam radiation therapy, radical prostatectomy, and watchful waiting in those in whom radical treatment is not suitable.

The Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy in Prostate Cancer (CHHiP) trial (CRUK/06/016) compared conventional and hypofractionated high-dose intensity modulated radiation therapy (HFRT) for PCa (2). The hypofractionated regimen of 60 Gy in 20 fractions was shown to be noninferior to the conventional fractionation of 74 Gy in 37 fractions, supporting its use as a new standard of care for external beam radiation therapy for PCa.

Although age is not a factor in the likelihood of a patient completing radiation therapy (3), elderly patients are generally underrepresented in clinical trials, resulting in the lack of a robust evidence base (4, 5). The median age in the CHHiP trial was 69 years (range, 44-85 years). This reflects the age-related incidence of PCa and the appropriate use of a patient's performance status rather than age to direct treatment decisions. In this exploratory analysis of the CHHiP data, we compare treatment outcomes in terms of time to biochemical or clinical failure (BCF) and treatment-related toxicity in patients categorized as aged < 75 years or ≥ 75 years.

Methods and Materials

Study design and randomization

The CHHiP study design has been described elsewhere (2). In brief, male patients aged ≥ 16 years with a World Health Organization performance status of 0 or 1 and

histologically proven T1bN0M0 to T3aN0M0 PCa were eligible. Patients with T3 tumors and a Gleason score ≥ 8 or with a life expectancy < 10 years were ineligible. Initially, men with a prostate-specific antigen (PSA) level ≤ 40 ng/mL and a risk of pelvic lymph node involvement $< 30\%$ were eligible, but this was revised in August 2006 to a requirement of PSA level < 30 ng/mL and a risk of seminal vesicle involvement $< 30\%$ to reflect the developing consensus of a need for long-term androgen deprivation therapy (ADT) in men with locally advanced disease. The trial was reviewed by the London Multicentre Research Ethics Committee (04/MRE02/10) and was in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki).

Men were randomized (1:1:1) to receive 74 Gy in 37 fractions over a period of 7.4 weeks (conventional fractionation) or 1 of 2 hypofractionated regimens using daily fractions of 3 Gy: 60 Gy in 20 fractions over a period of 4 weeks or 57 Gy in 19 fractions over a period of 3.8 weeks. Randomization was stratified for National Comprehensive Cancer Network (NCCN) risk classification and treatment center but not patient age. It was not possible to mask patients or clinicians to treatment allocation.

Procedures

Three to six months of ADT before and during radiation therapy was mandated in men with NCCN intermediate- and high-risk disease but was optional in those with low-risk disease. All radiation therapy was given using an intensity modulated radiation therapy technique. Further details of the treatment and its quality assurance have been reported previously (2). PSA concentrations were recorded before commencing ADT and radiation therapy and then at weeks 10, 18, and 26 after radiation therapy, after which they were recorded at 6-month intervals for 5 years and then annually.

Acute and late toxicity was assessed using clinician-reported outcome (CRO) grading systems and patient-reported outcome (PRO) questionnaires. The Radiation Therapy Oncology Group (RTOG) system (6) was used to score toxicity every week during radiation therapy and at weeks 10, 12, and 18. Bowel, bladder, and sexual function assessments were made before ADT and the start of radiation therapy and were graded according to the Late Effects on Normal Tissues: Subjective/Objective/Management (LENT/SOM) (7) and Royal Marsden Hospital (RMH) (8) scoring systems. Late toxicity was collected every 6 months for 2 years and annually thereafter until 5 years using all 3 toxicity scales. Men participating in a PRO substudy received questionnaires at baseline if they had not yet started ADT, and all men received questionnaires before radiation therapy and at 10 weeks and 6, 12, 18, and 24 months after the start of radiation therapy and then annually until 5 years was reached. Further details of the PRO substudy are presented elsewhere (9).

Outcomes

BCF was the primary endpoint. The Phoenix Consensus guideline of a PSA concentration greater than the nadir plus 2 ng/mL (10) was used after 2007 and applied retrospectively to patients recruited before this date. Other recurrence (failure) events included recommencement of ADT, local recurrence, lymph node or pelvic recurrence, and distant metastases. Acute toxicity was reported as the highest grade of bowel and bladder toxicity in the first 18 weeks from the start of radiation therapy. CRO late toxicity outcomes were reported using the time to first grade 2 or greater toxic effect using the RTOG, LENT/SOM, and RMH scoring systems. PROs of interest were time to first small or greater overall bowel bother and overall urinary bother reported as single items on the University of California, Los Angeles Prostate Cancer Index (UCLA-PCI) (11) and 50-item Expanded Prostate Index Composite (EPIC-50) (12) questionnaires.

Statistical considerations

All analyses presented are exploratory post hoc subgroup analyses. As this was a nonrandomized comparison, statistical comparisons were made for the baseline demographic data presented by age group (<75 years and ≥ 75 years) (t test, Mann-Whitney test, χ^2 test, and χ^2 trend test were used as appropriate). Kaplan-Meier methods were used to analyze time-to-event data. Comparisons of each hypofractionated regimen with the 74-Gy regimen were made within each age group using the log-rank test. Hazard ratios (HRs) < 1 favored hypofractionated radiation therapy. Acute and late toxicity data were analyzed using the same methods as previously described (2), with treatment comparisons made within each age group separately. Toxicity of grade 2 at 5 years from starting radiation therapy was of primary interest. PROs were analyzed using the same methods as previously described (9); small or greater bother was of primary interest. A significance level of 1% was used because of multiple testing. All analyses were conducted using Stata software (version 13.0; StataCorp) and were based on the primary analysis data snapshot taken on September 8, 2015.

Results

Baseline demographic data

The baseline demographic data of patients in the group aged < 75 years (n = 2725) and the group aged ≥ 75 years (n = 491) are shown in Table 1, and medical history information is shown in Table E1 (available online at www.redjournal.org). There was a significant difference ($P < .0001$) in NCCN risk group distribution between age groups, with a higher proportion of intermediate-risk disease than low-risk disease in the group aged ≥ 75 years. The group aged ≥ 75 years had more cancers with a

Table 1 Baseline demographic data of patients aged < 75 years and ≥ 75 years

	Age < 75 y (n = 2725)	Age ≥ 75 y (n = 491)	*P* value
Age, median (IQR), y	67 (63-71)	76 (75-78)	<.0001
Treatment group, n (%)			.709
74 Gy	898 (33)	167 (34)	
60 Gy	925 (34)	149 (30)	
57 Gy	902 (33)	175 (36)	
NCCN risk group, n (%)			<.0001
High risk	321 (12)	64 (13)	
Intermediate risk	1956 (72)	391 (80)	
Low risk	448 (16)	36 (7)	
Intended hormone therapy, n (%)			.014
LHRH-positive short-term AA	2264 (84)	436 (89)	
150 mg of bicalutamide	357 (13)	46 (9)	
MAB	3 (<1)	2 (<1)	
Bicalutamide—other	2 (<1)	0 (0)	
LHRH alone	0 (0)	2 (<1)	
None	86 (3)	4 (<1)	
Gleason score, n (%)			.018
≤6	975 (36)	147 (29)	
7	1668 (61)	327 (67)	
8	82 (3)	17 (4)	
Clinical T category, n (%)			<.0001
T1	1034 (38)	136 (28)	
T2	1452 (53)	314 (64)	
T3	236 (9)	41 (8)	
TX	1 (<1)	0 (0)	
Missing or not done	1 (<1)	0 (0)	
Prehormone PSA level			
No. with data	2724	490	
Median (IQR), ng/mL	9.8 (7.0-14.2)	11.4 (8.6-14.8)	<.0001
Prehormone testosterone level			
No. with data	1114	146	
Median (IQR), nmol/L	12.6 (9.5-16.2)	12.3 (9.5-16.4)	.883
Prehormone LH level			
No. with data	1033	123	
Median (IQR), IU/L	4 (3-6); range, 1-56	5 (3-7); range, 1-30	.024
IGRT used, n (%)			
Yes	825 (33)	148 (33)	.963
No	1686 (67)	304 (67)	
Prostate volume			
No. with data	936	217	
Median (IQR), cm^3	37.0 (28.0-50.0)	42.7 (30.3-54.8)	.001
Maximum length of core involvement			
No. with data	1451	289	
Median (IQR), %	35 (15-60)	40 (20-70)	.007
Maximum length of core involvement			
No. with data	452	92	
Median (IQR), mm	9 (4-17)	12 (7-20)	.007

Abbreviations: AA = Anti-androgen; IGRT = Image Guided Radiation Therapy; LH = Luteinising hormone; LHRH = Luteinising hormone releasing hormone; MAB = Maximal Androgen Blockade; NCCN = National Comprehensive Cancer Network; PSA = prostate-specific antigen.

Gleason score of 7 but fewer cancers with a Gleason score of 6 than the group aged < 75 years, and the group aged ≥ 75 years had a larger maximum length of biopsy core involvement. Median PSA levels were higher in the group aged ≥ 75 years (11.4 ng/mL) than in the group aged < 75 years (9.8 ng/mL, $P < .0001$), but prehormone testosterone levels were similar. Prostate volume was larger in the group aged ≥ 75 years (median, 42.7 cm^3) than in the group aged < 75 years (median, 37.0 cm^3; $P = .001$). More patients in the group aged ≥ 75 years than in the group aged < 75 years underwent a previous transurethral resection of the prostate (13% vs 7%, $P < .0001$; Table E1,

available online at www.redjournal.org). Image guided radiation therapy use was similar in the 2 groups, but more men in the group aged < 75 years received bicalutamide alone ($P = .014$).

Time to BCF

There was no evidence of a difference in BCF between the 2 age groups ($P = .909$) (Fig. 1 A). In the group aged < 75 years, the 5-year BCF-free rates were 88.9% (95% confidence interval [CI], 86.5%-90.9%), 90.5% (95% CI, 88.3%-92.3%), and 85.5% (95% CI, 82.8%-87.8%) in the 74-, 60-, and 57-Gy groups, respectively (Fig. 1 B). In the group aged ≥ 75 years, the 5-year BCF-free rates were 84.7% (95% CI, 77.3%-89.9%), 91.0% (95% CI, 83.7%-95.1%), and 87.7% (95% CI, 80.2%-92.4%) in the 74-, 60-, and 57-Gy groups, respectively (Fig. 1 C). The BCF-free rates for the 74-Gy group were slightly better in the group aged < 75 years than in the group aged ≥ 75 years (in keeping with less favorable presenting features in the group aged ≥ 75 years), which seemed to be favorably modified by hypofractionation (Fig. 1 C).

Acute toxicity

The prevalence of clinician-assessed bowel (Fig. 2 A) and bladder (Fig. 2 B) toxicity from week 1 to week 18 was similar in the 2 age groups. There was no evidence of a difference in peak acute RTOG bowel toxicity (Fig. 2 A) between age groups ($P = .561$), with 34 of 1859 patients (2%) in the group aged < 75 years and 5 of 289 patients (2%) in the group aged ≥ 75 years experiencing grade 3 bowel toxicity, with no reported grade 4 bowel toxicity. Within the group aged < 75 years, there was a significant difference in peak acute bowel toxicity between the control group and both hypofractionated groups ($P < .0001$ for both the 60- and 57-Gy comparisons); however, this did not reach statistical significance in the group aged ≥ 75 years ($P = .097$ for 60 Gy and $P = .054$ for 57 Gy) (Table E2, available online at www.redjournal.org). At 18 weeks, there was no significant difference in the distribution of the grade of acute bowel toxicity between age groups ($P = .274$).

There was no evidence of a difference in peak acute RTOG bladder toxicity (Fig. 2 B) between age groups ($P = .920$). Grade 3 toxicity and grade 4 toxicity were recorded in 147 of 1859 patients (8%) and 21 of 1859 (1%), respectively, in the group aged < 75 years and in 20 of 289 (7%) and 2 of 289 (1%), respectively, in the group aged ≥ 75 years. Within the group aged < 75 years, there was no significant difference in acute bladder toxicity noted between the control group and either hypofractionated group ($P = .969$ for 60 Gy and $P = .569$ for 57 Gy). However, within the group aged ≥ 75 years, there was more acute bladder toxicity in the control group than in the 60-Gy group ($P = .004$) but not the 57-Gy group ($P = .083$) (Table E2, available online at www.redjournal.org). The differences had disappeared by 18 weeks.

Late toxicity

There was no evidence of a difference in time to first grade ≥ 2 bowel toxicity using any CRO scale for either hypofractionated group compared with the control group in either age group (Fig. 3). The 5-year cumulative incidences of grade ≥ 2 RTOG, RMH, and LENT-SOM late bowel side effects were similar, with rates of 9.9% (95% CI, 8.8%-11.2%) versus 12.5% (95% CI, 9.5%-16.3%), 13.5% (95% CI, 12.2%-14.9%) versus 12.9% (95% CI, 10.0%-16.6%), and 20.4% (95% CI, 18.8%-22.1%) versus 20.4% (95% CI, 16.8%-24.7%), respectively, for the group aged < 75 years versus the group aged ≥ 75 years (Fig. 3). The prevalence of CRO late side effects was stable over time from 1 to 5 years, with 2-year grade ≥ 2 RTOG, RMH, and LENT-SOM bowel toxicity in 68 of 2430 patients (3%), 87 of 2413 (4%), and 131 of 2352 (6%), respectively, in the group aged < 75 years compared with 12 of 413 (3%), 21 of 412 (5%), and 29 of 401 (7%), respectively, in the group aged ≥ 75 years for the 74-, 60-, and 57-Gy schedules (Figs. E1-E3, available online at www.redjournal.org). Patient-reported small or greater bowel bother peaked at 10 weeks after the start of radiation therapy and was similar in both age groups (Figs. E4 and E5, available online at www.redjournal.org). At 2 years, the prevalence of small or greater bowel bother was 146 of 1159 patients (13%) in the group aged < 75 years and 28 of 153

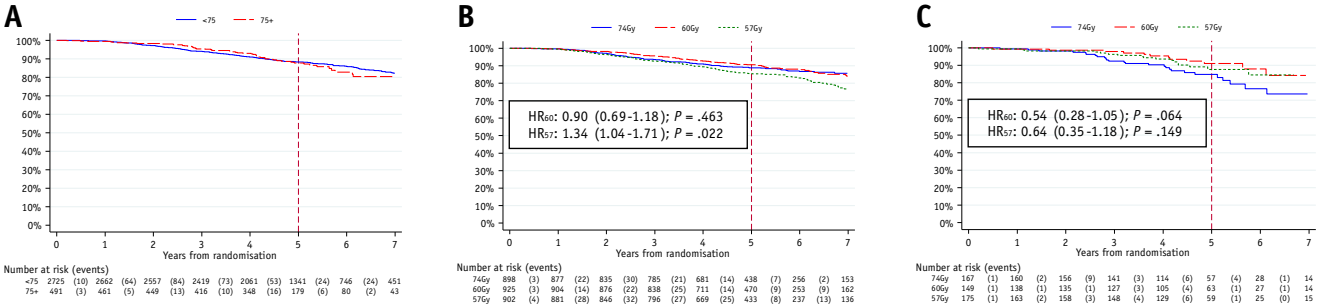

Fig. 1. Time to biochemical failure or prostate cancer recurrence for patients aged < 75 years and ≥ 75 years (A), patients aged < 75 years by treatment group (B), and patients aged ≥ 75 years by treatment group (C).

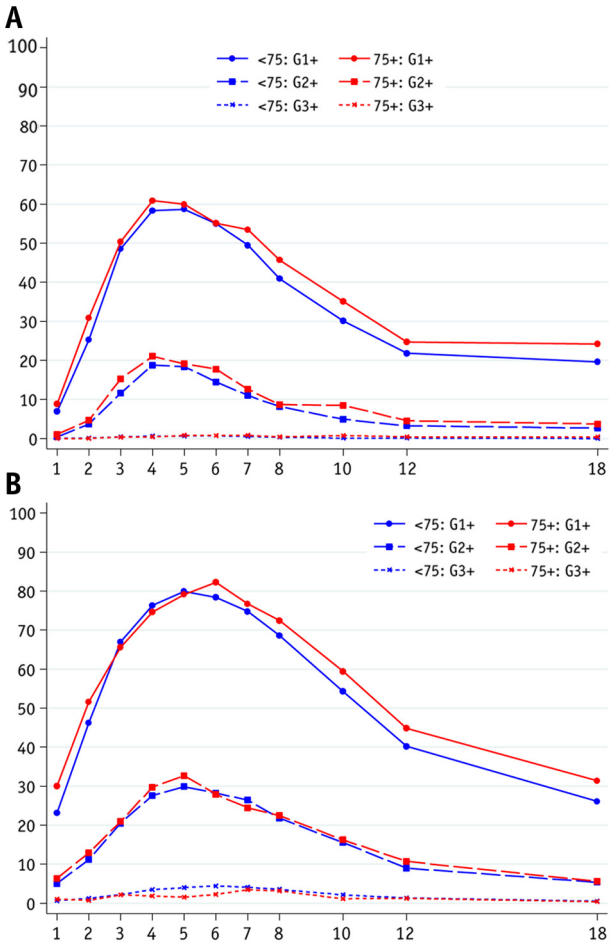

Fig. 2. Prevalence of clinician-assessed Radiation Therapy Oncology Group bowel (A) and bladder (B) toxicity during week 1 to week 18 from start of radiation therapy for patients aged < 75 years and ≥ 75 years by toxicity grade.

(18%) in the group aged ≥ 75 years, remaining slightly higher in the group aged ≥ 75 years at all time points to 5 years (Figs. E4 and E5, available online at www.redjournal.org), when the cumulative incidences of small or greater bowel bother were 32% (95% CI, 30%-35%) and 38% (95% CI, 32%-44%) in the groups aged < 75 years and ≥ 75 years, respectively. Although there was no evidence of a difference between the fractionation schedules in the group aged < 75 years, in the group aged ≥ 75 years, there was a suggestion of a higher cumulative incidence of small or greater bowel bother with 60 Gy compared with 74 Gy (HR, 1.44; 95% CI, 0.90-2.32; $P = .115$) or 57 Gy (HR, 0.81; 95% CI, 0.48-1.38; $P = .460$), but this did not reach the conventional level of statistical significance (Fig. 4 A).

There was no certain evidence of a difference in time to first grade ≥ 2 bladder toxicity using CROs for either hypofractionated group compared with the control group in either age group (Fig. 5). However, there was a suggestion of increased RTOG toxicity with 60 Gy in the group aged < 75 years ($P = .012$). The 5-year cumulative incidences of grade ≥ 2 RTOG, RMH, and LENT-SOM late bladder side effects were similar, with rates of 6.6% (95% CI, 5.7%-7.7%) versus 9.2% (95% CI, 6.9%-12.3%), 25.9% (95% CI, 24.2%-27.7%) versus 32.1% (95% CI, 27.6%-37.0%), and 38.1% (95% CI, 36.1%-40.1%) versus 40.5% (95% CI, 35.7%-45.7%), respectively, for the group aged < 75 years versus the group aged ≥ 75 years (Fig. 5). The 2-year prevalence of grade ≥ 2 RTOG, RMH, and LENT-SOM bladder toxicity was 32 of 2430 patients (1%), 193 of 2417 (8%), and 287 of 2346 (12%), respectively, in the group aged < 75 years compared with 8 of 413 (2%), 39 of 410 (10%), and 54 of 399 (14%), respectively, in the group aged ≥ 75 years and was stable over time (Figs. E6-E8, available online at www.redjournal.org). Grade 1 RMH bladder symptoms were persistently greater in the group aged ≥ 75 years both before and after treatment (Fig. E7 A, available online at www.redjournal.org). Patient-reported small or greater bladder bother peaked at 10 weeks after the start of radiation therapy and was similar in both age groups (Figs. E9 and E10, available online at www.redjournal.org). At 2 years, the prevalence of small or greater bladder bother was 140 of 1154 patients (12%) and 33 of 149 (22%) in the groups aged < 75 years and ≥ 75 years, respectively, remaining slightly higher in the group aged ≥ 75 years at all time points to 5 years (Figs. E9 and E10, available online at www.redjournal.org), when the cumulative incidences of small or greater bladder bother were 30% (95% CI, 28%-33%) and 39% (95% CI, 33%-46%) in the groups aged < 75 years and ≥ 75 years, respectively. Although there was no difference between the fractionation schedules in the group aged < 75 years, there was a suggestion of a lower cumulative incidence of small or greater bladder toxicity with 57 Gy compared with 74 Gy (HR, 0.71; 95% CI, 0.43-1.16; $P = .163$) or 60 Gy (HR, 1.01; 95% CI, 0.63-1.62; $P = .953$) in the group aged ≥ 75 years (Fig. 4 B).

At 2 years, the incidence of LENT/SOM grade ≥ 2 sexual dysfunction was 1402 of 2189 patients (64%) and 262 of 360 (73%) in the groups aged < 75 years and ≥ 75 years, respectively; at 5 years, the incidence was 825 of 1255 (66%) and 109 of 161 (68%), respectively. The increased incidence of erectile dysfunction in the group aged ≥ 75 years predated hormone and radiation therapy and persisted for the 5 years of follow-up (Fig. E11, available online at www.redjournal.org). There was no evidence of a difference in time to grade ≥ 2 erectile dysfunction between the fractionation schedules in either age group (Fig. E12, available online at www.redjournal.org).

Discussion

The poor recruitment of older adults into clinical trials is thought to be due to functional reserve decline, increased comorbid conditions, lack of social support, and increased concomitant medications in elderly patients (13). When making decisions about their cancer treatment, older

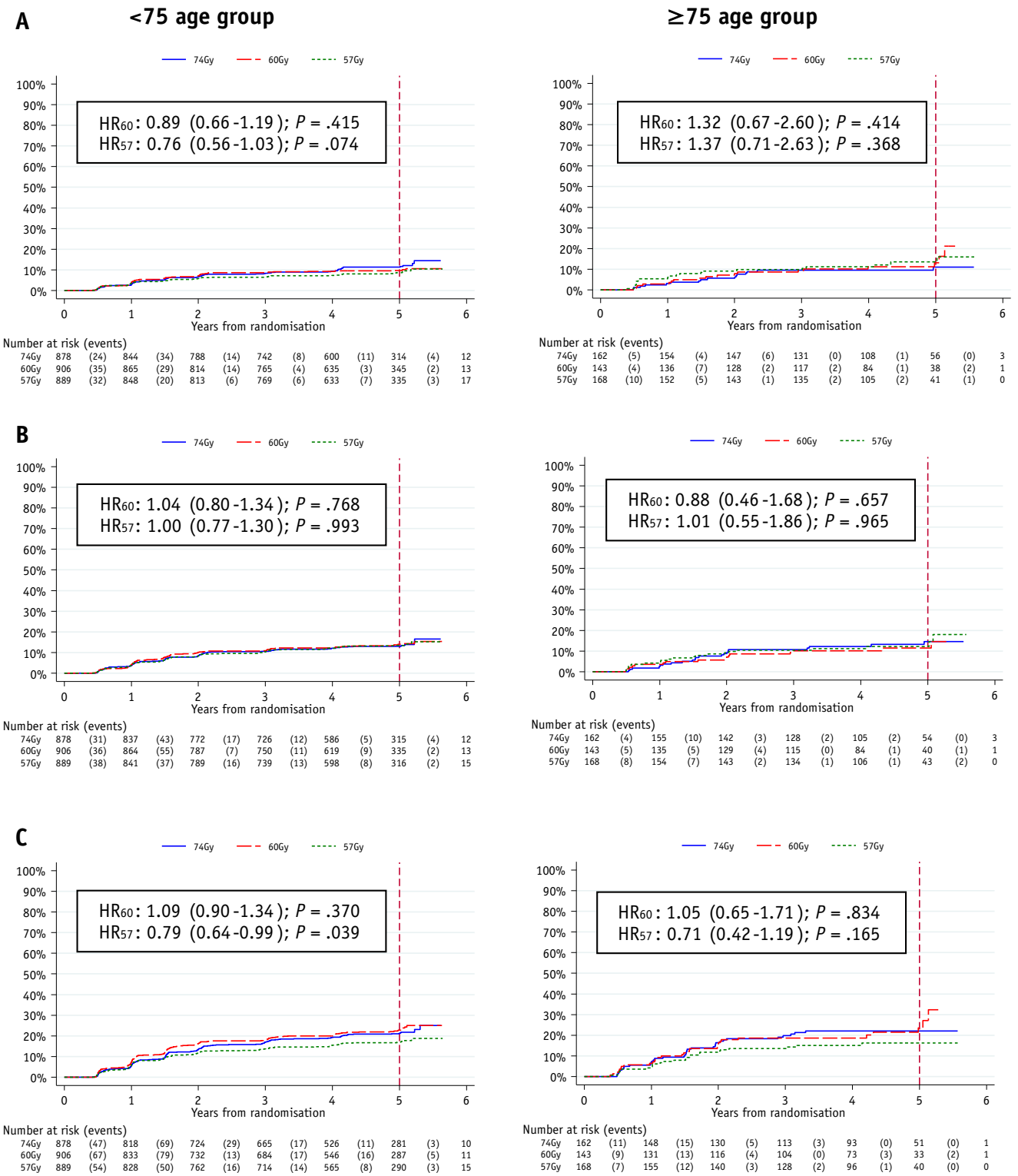

Fig. 3. Time to first grade ≥ 2 bowel toxicity assessed by Radiation Therapy Oncology Group (A), Royal Marsden Hospital (B), and Late Effects on Normal Tissues: Subjective/Objective/Management (C) scales for patients aged < 75 years and ≥ 75 years by treatment group.

patients also have concerns about treatment-related discomfort, fear of side effects, and transport issues (14). In an elderly population, the patient's functional status and the presence of "geriatric syndromes" such as dementia, depression, osteoporosis, or falls are associated with increased chemotherapy toxicity (15). Data on radiation therapy outcomes and toxicity in an elderly population are sparse.

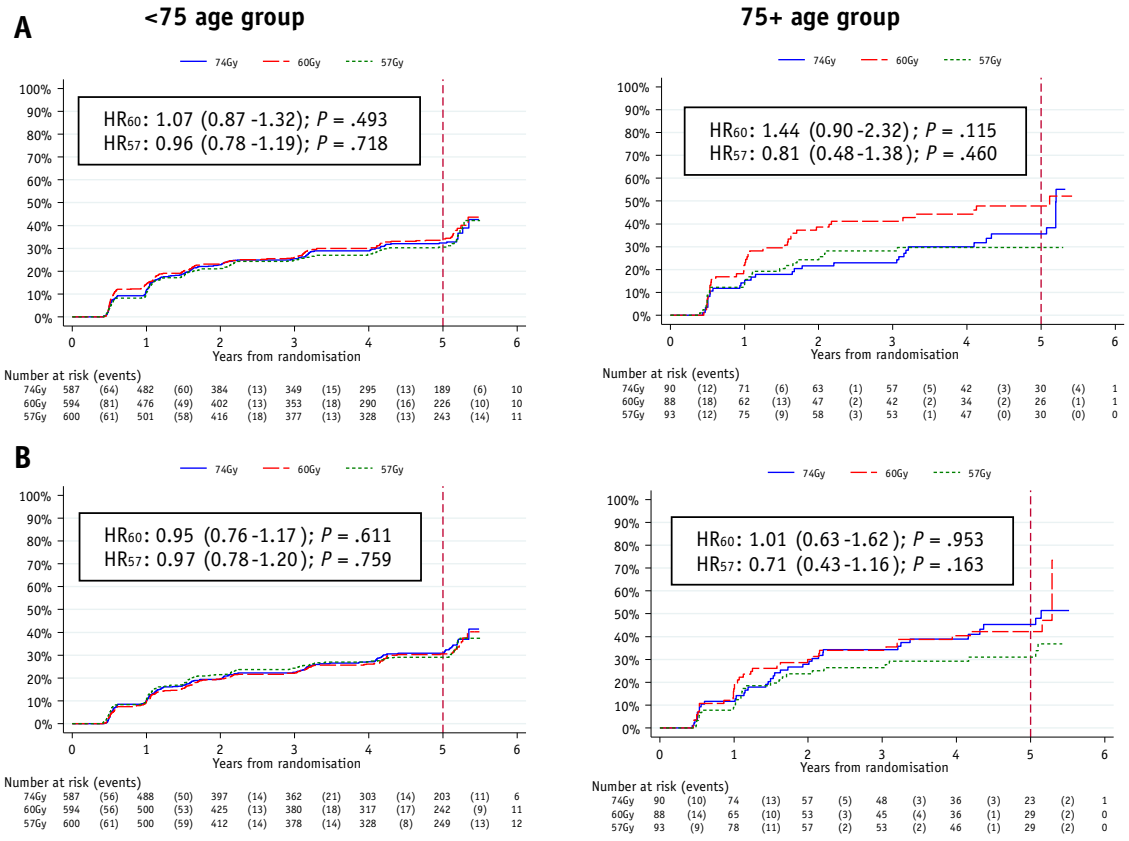

Fig. 4. Time to first small or greater bowel (A) and urinary (B) bother for patients aged < 75 years and ≥ 75 years by treatment group.

In this post hoc subgroup analysis of the CHHiP trial, there was no evidence of a difference in BCF in the group aged < 75 years and the group aged ≥ 75 years. Results in the group aged < 75 years mirrored the findings in our previous report (2), with higher BCF rates in the 57-Gy randomized trial arm. However, in the group aged ≥ 75 years, both 60 Gy and 57 Gy showed higher (91.0% and 87.7%, respectively) 5-year BCF-free outcomes than 74 Gy (84.7%), although this was not statistically significant. Equivalent results were seen in the group aged ≥ 75 years and the group aged < 75 years despite less favorable features at presentation. This imbalance of prognostic factors between age groups may relate to clinician or patient preference for an active surveillance strategy with increasing age as observed previously in a Canadian population-based study (16). We are not aware of any previous evidence of a relatively beneficial effect of hypofractionated radiation therapy in older patients with PCa. This could have resulted from an imbalance of other unmeasured prognostic factors or perhaps slower or incomplete testosterone recovery. Alternatively, it may be a chance finding owing to the relatively small proportion of elderly patients (15% of the overall trial population). Although noninferiority of 57 Gy compared with 74 Gy could not be claimed formally in the whole trial population (5-year control rate of 85.9% vs 88.3%), the 57-Gy schedule has potential advantages in that it may moderate long-term side effects without a meaningful compromise of treatment efficacy in elderly patients. The 57-Gy schedule has recently been endorsed by an NHS England guidance for consideration in frail elderly patients (17).

Previously, one study in a mixed cohort of patients aged > 70 years showed no increase in grade 3 to 4 toxicity in more vulnerable or frail patients (5). To our knowledge, our study is the first assessment of both CROs and PROs in elderly patients with PCa treated with HFRT. While this was not a preplanned analysis and results must be regarded as exploratory, the large number of patients recruited to the CHHiP trial permits some observations. There was no increase in peak acute bowel or bladder toxicity in the group aged ≥ 75 years compared with the group aged < 75 years, and HFRT appeared well tolerated in elderly patients. The difference in acute bowel toxicity between the control and HFRT groups seen in the group aged < 75 years ($P < .0001$ for both 60- and 57-Gy comparisons) failed to reach statistical significance in the group aged ≥ 75 years. This finding is reassuring but most likely relates to the smaller sample size in the group aged ≥ 75 years. It is important to note that 18 weeks after radiation therapy, acute bowel toxicity had settled satisfactorily in both age cohorts, with no differences between the fractionation schedules. With respect to acute bladder toxicity, there was a significant increase in

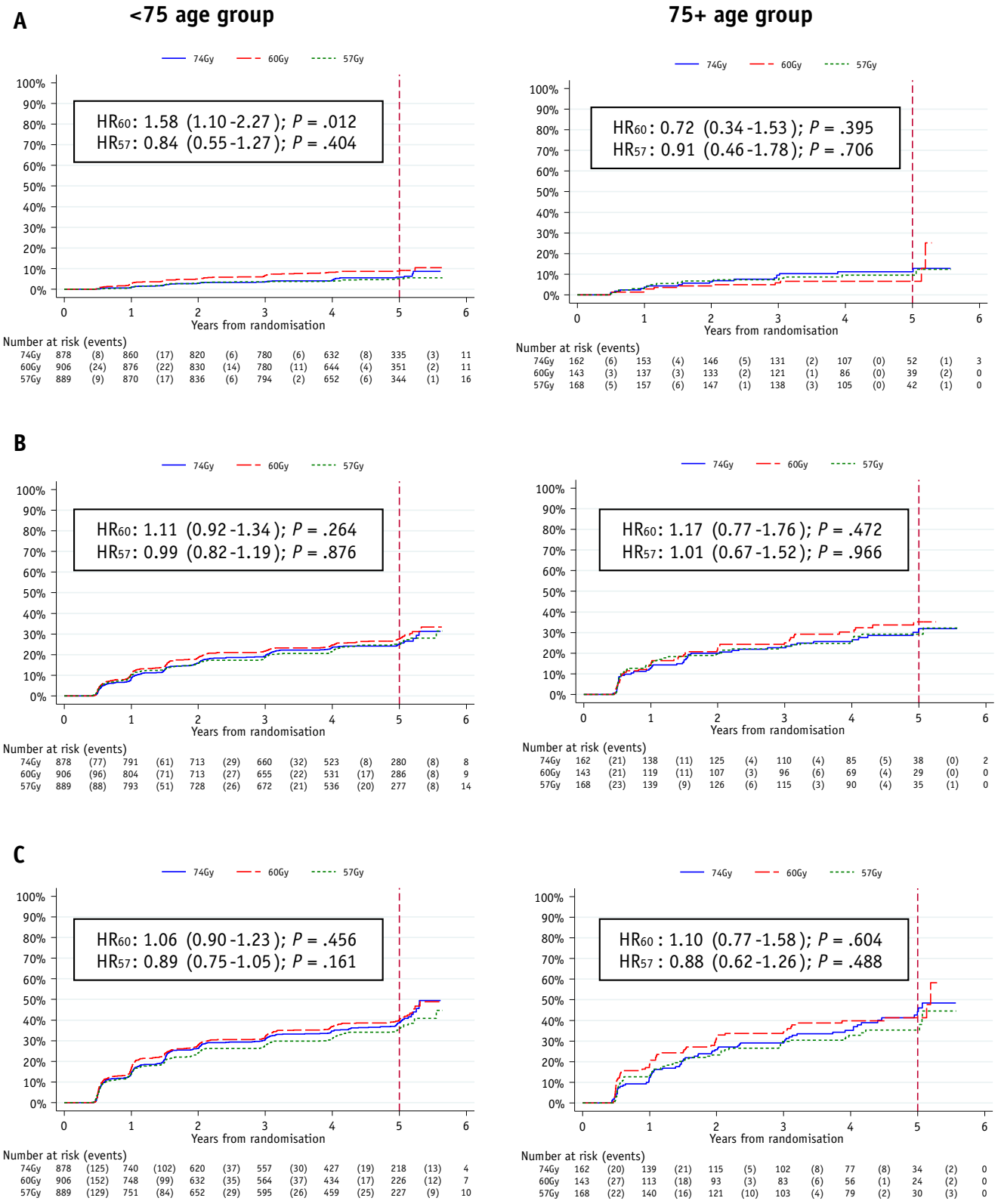

Fig. 5. Time to first grade ≥ 2 bladder toxicity assessed by Radiation Therapy Oncology Group (A), Royal Marsden Hospital (B), and Late Effects on Normal Tissues: Subjective/Objective/Management (C) scales for patients aged < 75 years and ≥ 75 years by treatment group.

RTOG grade ≥ 2 toxicity between the control group and 60-Gy group ($P = .004$) but not the 57-Gy cohort ($P = .083$) in the group aged ≥ 75 years. This difference was not seen for the group aged < 75 years (Table E2, available online at www.redjournal.org). This finding might reflect a higher incidence of pretreatment bladder dysfunction and support use of the regimen of 57 Gy in 19 fractions in older men, particularly as this schedule was not associated with a decrease in treatment efficacy compared with 74 or 60 Gy.

There were no consistent differences in the prevalence or cumulative incidence of CRO late bowel toxicity up to 5 years after radiation therapy between the groups aged $<$ 75 years and ≥ 75 years. Similar findings were seen using conventional radiation therapy or HFRT and assessments with the RTOG, RMH, or LENT-SOM instruments. However, with the use of PROs, there was a consistent increase in reporting of bowel bother in the group aged ≥ 75 years, and this appeared to be most pronounced in the 60-Gy group rather than the 74- or 57-Gy cohort. Fractionation schedule was not related to bowel bother in the group aged < 75 years.

There appeared to be more bladder symptoms in the group aged ≥ 75 years compared with the group aged < 75 years at 5 years measured by the CRO instruments. This was confirmed using PROs, and all degrees of bladder bother were increased in the group aged ≥ 75 years. Fractionation schedule appeared unrelated to bladder bother in the group aged < 75 years, but 57 Gy appeared to be associated with reduced bother scores in the group aged ≥ 75 years rather than those patients treated with 74 Gy and 60 Gy, although this failed to reach statistical significance. Although it is difficult to separate treatment effects from an increase in urinary symptoms in an elderly population, this might sound a cautionary note against dose escalation in more aged patients.

Erectile dysfunction was increased after treatment in the group aged ≥ 75 years. This finding was expected as increasing age has previously been identified as a risk factor for erectile dysfunction following ADT and radiation therapy for PCa (18). Higher levels of dysfunction were scored using the LENT-SOM instrument compared with using PROs to assess bother, perhaps reflecting the change in importance of erectile dysfunction with increasing age. However, post-ADT testosterone recovery may be delayed and incomplete in older patients. As having a normal testosterone level is important in the recovery of erectile dysfunction, as well as other health issues, it is recommended that this should be assessed after treatment (19).

Conclusions

HFRT using 60 or 57 Gy delivered in 3-Gy fractions appears to be well tolerated and effective in more elderly men, and age should not be a barrier to implementing shorter radiation therapy schedules. The 57-Gy schedule has potential advantages in moderating long-term bowel and bladder side effects while maintaining satisfactory PCa control.

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